REMARKS

Claims 1, 12-19, 30, 51 and 52 are pending. Claims 1 and 30 have been amended to return element (D) to the original scope. Claims 1 and 30 differ from original claims 1 and 30 in reciting that the first targetable conjugate necessarily comprises an enzyme. Claim 20 has been canceled. Claims 51 and 52 have been amended to clarify that are directed to (D)(1) and (D)(2), respectively. Claims 53 and 54, corresponding to canceled claims 2 and 31, have been added. While the independent claims have been amended, and the number of pending claims has been increased by one, entry and consideration of the foregoing amendments is respectfully solicited. In particular, it is believed that no new issue requiring further search has been raised because the claims still require a first targetable conjugate that comprises an enzyme, as they did after applicants' previous amendment, and that this claim scope already has been found to distinguish over the art of record. In compliance with 37 C.F.R. § 1.121(b & c), Applicants enclose marked up versions of the amended claims and pages 26, 27 and 29, showing all of the relative changes. Support for these amendments can be found in the original claims. Claims 1, 12-19, 30 and 51-54 are pending.

The Examiner rejects claims 1, 12-20 and 30 under 35 U.S.C. §112, ¶2, for allegedly being indefinite. The claims as amended set forth the functional relationship between the enzyme and the drug or prodrug. Claim 20 has been canceled. Reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner rejects claims 1, 12-20 and 30 under 35 U.S.C. §112, ¶1. Applicants have amended the claims to address the issues raised by the examiner and respectfully request reconsideration and withdrawal of this rejection.

Previously, the examiner rejected claims 1, 9, 16, 18-20, 32 and 34 under 35 U.S.C. §102(a), for allegedly being anticipated by Gautherot *et al.*; claims 1, 3, 9, 12-16, 18-19, 24-29 and 32-34 under 35 U.S.C. §102(a), for allegedly being anticipated by Karacay *et al.* (*Proceedings of the American Association for Cancer Research Annual Meeting*)("Karacay I"); claim 30 under 35 U.S.C. §102(a), for allegedly being anticipated by Karacay *et al.* Karacay I; claims 1, 3, 9, 12-16, 18-19, 24-30 and 32-34 under 35 U.S.C. §102(a), for allegedly being anticipated by Karacay *et al.* (*J. Nuc. Med.*)("Karacay II"); claims 1, 9, 16, 18-19, 32 and 34 under 35 U.S.C. §102(b), for allegedly being

anticipated by Bardies *et al.*; claim 30 under 35 U.S.C. §102(b), for allegedly being anticipated by Gautherot *et al.* or Bardies *et al.*; claims 1, 3, 6-7, 9-10, 12-13, 16, 18-19, 32 and 34 under 35 U.S.C. §102(b), for allegedly being anticipated by Barbet *et al*; claim 30 under 35 U.S.C. §102(b), for allegedly being anticipated by Barbet *et al.*; and claims 1, 3, 6-7, 9, 12-13, 18-19, 30, 32 and 34 under 35 U.S.C. §102(b), for allegedly being anticipated by Goodwin *et al.* The examiner also rejected claim 30 under 35 U.S.C. §103(a), for allegedly being unpatentable over Gautherot *et al.* or Bardies *et al.*; rejects claim 30 under 35 U.S.C. §103(a), for allegedly being unpatentable over Karacay I; claims 1, 9 and 11 under 35 U.S.C. §103(a), for allegedly being unpatentable over Barbet *et al.* or Goodwin *et al.*, either in view of Griffiths; claims 1, 14-15 and 32-33 under 35 U.S.C. §103(a), for allegedly being unpatentable over Bardies *et al.*, Gautherot *et al.*, Barbet *et al.*, or Goodwin *et al.*, any in view of Goldenberg; claims 1 and 8 under 35 U.S.C. §103(a), for allegedly being unpatentable over Barbet *et al.* or Goodwin *et al.*, either in view of Kondratyev; and claims 1 and 20 under 35 U.S.C. §103(a), for allegedly being unpatentable over Barbet *et al.* or Goodwin *et al.*, either in view of Huston *et al.* The examiner also provisionally rejects claims 1 and 4-5 under 35 U.S.C. §103(a), for allegedly being unpatentable over copending Application No. 09/205,243 in view of Barbet *et al.* or Goodwin *et al.*

Applicants submit that the amended claims still obviate the rejections. In particular, all of the documents describe the use of bispecific antibodies and radiolabelled bivalent haptens, and none of them disclose or suggest administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate and a first targetable conjugate which comprises a carrier portion and one or more conjugated enzymes, wherein said carrier portion comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and then administering either (1) a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site; or (2) a drug which is capable of being detoxified in said patient to form an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or (3) a prodrug which is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, when said

enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or (4) a second targetable conjugate which comprises a carrier portion which comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site. Accordingly, Applicants respectfully submit that the present claims still are patentable over the previously cited documents.

In view of the foregoing remarks it is believed that the application is in condition for allowance. A favorable disposition of the application therefore is solicited. Examiner Saunders also is courteously invited to contact the undersigned if any questions remain or if he believes that further discussion will advance prosecution.

Respectfully submitted,

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November 25, 2002
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MARKED UP VERSION OF CLAIM AMENDMENTS

1. (Twice Amended) A method of treating diseased tissues in a patient, comprising:

(A) administering to said patient a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate;

(B) optionally, administering to said patient a clearing composition, and allowing said composition to clear non-localized antibodies or antibody fragments from circulation;

(C) administering to said patient a first targetable conjugate which comprises a carrier portion and one or more conjugated enzymes, wherein said carrier portion comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment; and

(D) administering to said patient [a second targetable conjugate which comprises a carrier portion and a prodrug, wherein said carrier portion comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment]

(1) a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site; or

(2) a drug which is capable of being detoxified in said patient to form an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or

(3) a prodrug which is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or

(4) a second targetable conjugate which comprises a carrier portion which comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and a prodrug, when said enzyme is capable of

converting said prodrug to a drug at the target site.

30. (Twice Amended) A kit useful for treating diseased tissues in a patient comprising:

(A) a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate;

(B) a first targetable conjugate which comprises a carrier portion and one or more conjugated enzymes, wherein said carrier portion comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment; [and]

(C) optionally, a clearing composition useful for clearing non-localized antibodies and antibody fragments; and

(D) [a second targetable conjugate which comprises a carrier portion and a prodrug, wherein said carrier portion comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment]

(1) a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site; or

(2) a drug which is capable of being detoxified in said patient to form an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or

(3) a prodrug which is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or

(4) a second targetable conjugate which comprises a carrier portion which comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and a prodrug, when said enzyme is capable of

converting said prodrug to a drug at the target site.

51. (Amended) The method of claim 1, wherein (D) comprises administering a prodrug and said enzyme is capable of converting said prodrug to a drug at the target site.

52. (Amended) The method of claim 1, wherein (D) comprises administering [said] a prodrug that is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, and said enzyme is capable of reconverting the detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site.